Roche

July 22, 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. 2005D-0183; Comments on the "Draft Guidance for Industry on Antiviral Drug Development—Conducting Virology Studies and Submitting the Data to the Agency," *Federal Register,* Volume 70, No. 100, Pages 30127-30128 (May 25, 2005)

Dear Sir or Madam:

Hoffmann-La Roche, Inc. has a long history of research, development and commercialization of anti-viral products. Given our interest and experience in the development of antiviral products we are pleased to have the opportunity to provide comments on the above referenced guidance document for the Agency's consideration.

We have provided our comments organized in the following sequence, General Comments, Major Comments, and Other Comments. Each is listed by section of the draft guidance and includes line numbers from the Draft Guidance in order to facilitate your review.

GENERAL COMMENTS:

- The Agency should consider including a separate section in this guidance document that addresses emerging/Novel targets. It would be helpful if the Agency could more explicitly indicate that the proposals for resistance testing included in this guidance document may not always apply to all agents or to biologics like interferon. We would also support the development of a separate guidance specifically focused on interferons and immunomodulatory drugs.
- We recognize that this guidance document is focused on requirements for virology studies as part of the development program for new/investigational compounds. We believe the burden of in vitro antiviral activity testing belongs with the new/investigational compound under development and that Sponsors of marketed products should not be required to generate duplicate in vitro activity data for the marketed compound in combination with investigational/newly approved agents.
- This guidance document should make clear that during the course of a development program the in vitro data will become less relevant as in vivo data become available. Although in vitro data may offer valuable insights into potential clinical observations, the in vitro situation cannot adequately imitate the effects of factors such as metabolic processes and other interactions that are encountered in vivo. Consequently, data generated in the clinical or in vivo situation will be more pertinent to clinical use and should supersede that generated in vitro. Our position is that the Agency should take into consideration the relative importance of generating additional in vitro data for products which have been marketed for a significant period of time and for which

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extensive clinical data exist, particularly where clinical data in the relevant scenario already exist, and the retrospective generation of in vitro data would not affect treatment decision-making.

- It is important that the final language and subsequent application of this guidance document continue to reflect that this is "guidance" and as such the Agency should remain flexible in the application of these principles since one cannot apply a uniform approach to all molecules and situations. Any Agency request for data should always be balanced and reflective of the circumstances of the trial and the target patient population.
- We applaud the Agency's efforts to bring together in one guidance document the fruits of early interactions with key stakeholders (including sponsors, diagnostics developers, vendors, key opinion leaders). We believe it is critical, given the nature of this dynamic field of research that the DAVDP continue to have an open dialogue and exchange of ideas/concerns/advances with all key stakeholders moving forward.

MAJOR COMMENTS:

2. Antiviral Activity:

Lines 221-232: *Inhibitory Quotient*

"Information on plasma and intracellular drug concentrations is important in assessing the dose/response of antiviral therapy and evaluating the potential for resistance development; therefore it is useful to determine an inhibitory quotient (IQ). (For more information on determining the IC_{50} values, see Section III.B.l2.a, Antiviral activity in vitro.) We view IQ rations as a useful too integrating in vivo drug concentrations and antiviral activity. It is a measure that characterizes the relationship between drug exposure and the susceptibility of a virus to a drug. A high IQ indicates an effective drug concentration can be achieved in a patient to inhibit the virus and minimize the development of drug resistance. Since one dose may not be adequate for all patient populations, IQ ratios can be used to aid in the selection of a dose or doses to further evaluate in phase 3 clinical studies."

We believe this section should be deleted from the guidance document for the reasons outlined below. We recognize that common practice in industry is the calculation of a Cmin threshold exceeding several fold the protein adjusted IC_{50} or IC_{90}, however, inhibitory quotient values are very dependent on how the IQ data are generated and on the method of calculation. Unless precise details of methodology and calculation are standardized and followed, misleading or inappropriate comparisons between products may be made [reference attached Poster from the 5th International Congress on Drug Therapy in HIV Infection (Glasgow, UK October 22-26, 2000) entitled "Prediction of drug potency from Cmin/IC ration: false precision?" Andrew Hill, Craig C, Whittaker L]. In addition, the Agency states that they view IQ ratios as "a useful tool". We believe the IQ is relevant for individual compounds to assist in the design of a development program but that it is not appropriate and/or relevant to compare compounds based on IQ since multiple other factors influence the efficacy of a product.

4. In Vitro Combination Activity Analysis

Lines 280-286: *"However, the interactions of drugs are complex and can result in antagonistic, additive, or synergistic effects with respect to antiviral activity. For this reason, we recommend that*

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sponsors evaluate the in vitro antiviral activity of investigational drugs in two- or three-drug combinations with other drugs approved for the same indication. We also recommend completing the in vitro drug combination activity studies of approved drugs with the investigational drug prior to initiation of the clinical trials that will evaluate the efficacy of the combination of the investigational drug with approved drugs."

While we appreciate the Agency's need to understand the interaction between compounds, we believe there is a lack of standardization of the conduct and control of in vitro combination experiments, which affects the results and conclusions generated. Interpretation algorithms vary and are not necessarily predictive of the clinical scenario where 2 and 3 drug combinations may be administered, including drugs for different indications. In vitro testing cannot mimic the pharmacological effects of the combinations that will be encountered in vivo, making interpretation and extrapolation to the clinical situation very tenuous. We recommend testing a minimal number of combinations of relevant drugs, after consultation with the agency, to flag early potential critical issues, but ultimately, pertinent in vivo or clinical information will supersede in vitro combination data.

OTHER COMMENTS:

Section II - Background

Lines 40-42: *"Because of the experience, history, and lessons learned with HIV-1 studies, this guidance focuses on studies commonly used to evaluate HIV-1 drugs and uses them as a paradigm for future studies of drugs to treat other viruses."*

Although some general principles apply, the guidance provided in this document may not be appropriate and/or applicable to acute viral disorders such as SARS or influenza. The Agency should consider either issuing guidances specific to the illness or virus type/family or making this guidance a set of general principles rather than applying the guidance based on HIV/hepatitis virus to all of the other viral illnesses, particularly those with shorter durations but potentially high mortality (e.g., SARS, pandemic influenza). One suggestion might be to expand the list of viral diseases in this guidance document for which a sponsor should initiate specific discussions with the Agency on the virology program (similar to the orthopox viruses).

Section III – Nonclinical Virology Reports

A. Overview:

Lines 68-70: *"In these cases, it is desirable to have in vitro combination activity studies designed to identify possible negative interactions on antiviral activity (i.e., antagonism) of the investigational drug with other antiviral drugs."*

This paragraph should acknowledge that antagonism is not always identified in in vitro testing.

Lines 77-81:

- *"Determining the antiviral activity of an investigational drug against viruses resistant to other drugs with the same molecular target"*
- *"Determining the antiviral activity of approved drugs against viruses resistant to the investigational drug with the same molecular target"*

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Clarity is required around these two bullets. We believe the term "relevant" should be inserted to revise the statement to suggest that drugs should be tested against "relevant viruses" and that given the fact that there are often multiple mutations involved in the generation of resistance, a representative sample of isolates should be tested.

B. Recommended Components of Nonclinical Virology Reports
1. Mechanism of Action:

Lines 138-140: *"We recommend consulting the DAVDP for specific advice regarding the development of immunomodulatory drugs for the treatment of viral diseases."*

We believe the phrase *"as well as products with other non viral host targets"* should be added to the end of the sentence listed above.

2. Antiviral Activity:

Lines 152-158: *"Additionally, in vitro antiviral activity and cytotoxicity assessments (see Section III.B.3., Cytotoxicity/Therapeutic Index) can be used to guide the selection of appropriate dose ranges in early clinical trials by establishing a dose/response relationship using a broad range of relevant cell types and virus isolates. If possible sponsors are encouraged to obtain antiviral activity data using primary human target cells. Because of viral genetic variation, the antiviral activity of the investigational drug should be examined for multiple clinical isolates and viral isolates representative of the virus population in clinical trials."*

In this section the Agency makes reference to "a broad range of relevant cell types and virus isolates" and "multiple clinical isolates and viral isolates". It would be helpful to the sponsor if the agency could list preferred or recommended cell types and virus isolates and if the Agency could give a range for the number of clinical and viral isolates to be examined (this range has varied for some products from as few as 20 to numbers in the thousands).

Lines 164-166: *"Evaluating the antiviral activity of the investigational drug against mutant viruses that are resistant to drugs with the same molecular target as the investigational drug as well as viruses resistant to other drugs for the same indication"*

We believe this statement should be modified as follows: "...as well as a limited number or representative sample of viruses resistant to other drugs for the same indication".

Line 191-195: *"Cell-based assay and host cell lines for studying viruses such as hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) replication may advance and improve, but at the present time are limited. For analysis of HCV replication, a replicon system ahs been developed that permits studies of viral replication and can be used to assess antiviral activity of some anti-HCV drugs."*

It should be noted in the guidance that the replicon system, while not validated is currently the in vitro model of choice for HCV drug development.

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Line 219: *"Sponsors are also encouraged to determine IC_{50} values in the presence of 2mg/mL α-acidic glycoprotein."*

We suggest the Agency reword this sentence as follows: "Sponsors are also encouraged the IC_{50} values in the presence of appropriate **disease related** levels of α-acidic glycoprotein (**e.g.,** 2 mg/mL **for HIV indications**)"

3. Cytotoxicity/Therapeutic Index

Lines 259-261: *"We recommend determining CC_{50} values in both stationary and dividing cells from multiple human cell types and tissues for potential cell-cycle, species, or tissue-specific toxicities."*

We suggest adding the term "relevant" before "Multiple human cell types". We also suggest the Agency provide suggested cell lines from which to choose to add further standardization within the field.

Lines 270-273: *"Therefore, it is important to monitor the effects of certain investigational drugs (e.g., nucleoside analogs) on mitochondrial toxicity by examining mitochondrial morphology, glucose utilization, lactic acid production, and mitochondrial DNA content."*

We believe the Agency should clarify that they are providing examples in this section and that sponsor should choose the tests that are relevant to their compound. Because there is overlap between some of the tests (e.g., mitochondrial DNA content is also predictive of lactic acid production), we do not believe it was the Agency's intent to have Sponsors use all of the methods for testing mitochondrial toxicity listed in this section of the guidance. As such we recommend editorial changes to the sentence as follows: "Therefore, it is important to monitor the effects of certain investigational drugs (e.g., nucleoside analogs) on mitochondrial toxicity (**e.g.,** mitochondrial morphology, glucose utilization, lactic acid production, **or** mitochondrial DNA content).

5. Resistance

Lines 304-336: *"Selection in cell culture of virus resistant to the investigational drug can provide insight into whether the genetic threshold for resistance development is high or low. Several factors specific to the investigational drug and the target virus affect the development of resistance (e.g., drug concentration). For some drugs, the development of resistance in the presence of high concentrations of the investigational drug occurs as a result of a single viral mutation whereas others require multiple mutations in the virus. A product with a low genetic threshold may select for resistance with only one or two mutations. In contrast, a product with a high genetic threshold may require several mutations to result in viral strains with reduced susceptibility. The rate of appearance of mutant viruses is dependent upon the rate of replication of the virus, the number of virus genomes produced, the fidelity of the replicative machinery, and host factors. Consideration of these factors can help in designing tests to detect the appearance in vitro of virus resistant to high concentrations of the drug. For example, many cell culture systems do not produce sufficient virus titers in those instances where multiple mutations are required to develop resistance to high concentrations of the investigational drug. In these instances, serial passage of the virus in cell culture under conditions of increasing concentrations of the investigational drug can lead to the isolation of resistant virus. Sponsors are encouraged to assess the development of resistance in vitro over the concentration range spanning the anticipated in vivo concentration and to determine*

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if the same or different patterns of resistance mutations develop by repeating the selection of variants resistant to the investigational drug several times."

As pointed out by the Agency a number of different factors, including drug concentration, are involved with development of resistance. These factors differ between the clinical and in vitro situations. Resistance is examined as a surrogate for "durability" of response and cannot be measured simply as the number of mutations needed for reduced phenotypic susceptibility as measured in an in vitro assay. Durability of response and the evolution of resistance are related to the degree of viral replication which is able to take place in the presence of the antiviral agent(s) and are therefore subject to the influence not only of the drug being assessed, but also of other antiretrovirals in a patient's regimen. Viral replication and the evolution of resistance in the presence of a given ARV will be influenced by the difficulty of getting mutations (e.g., debilitating effects on the ability of the virus to replicate and the requirement to acquire 'compensatory' mutations), the genetic background of the patient's virus and the number of mutations needed for a reduction in phenotypic susceptibility high enough to overcome prevailing plasma concentrations achieved in vivo. For these reasons we believe that interpretation of resistance data generated in vitro, such as by passage in the presence of fixed and/or arbitrary concentration of drug must be done with caution as it is important for prescribing physicians to understand that it is not necessarily predictive of what will be seen in the clinic.

Lines 347-349: *"In the case of larger viruses, we suggest that the relevant portions of the viral gene targeted by the investigational agent be sequenced and analyzed for mutations that could contribute to drug resistance."*

We believe the term "relevant" should be added so the statement would read "...sequenced and analyzed for **relevant** mutations that could contribute to drug resistance."

Line 381: *"Well-characterized genotypic and phenotypic assays should be developed to detect the emergence of resistant virus during the development of candidate drugs."*

The Agency should include a statement in this section of the guidance document indicating that it is important to try to correlate genotypic or phenotypic resistance to clinical virologic failure.

Lines 382-383: *"Sponsors can choose to conduct phenotypic and genotypic analyses themselves or send samples to a third party certified by Clinical laboratory Improvement Amendments (CLIA)."*

Does the Agency recognize laboratories outside of the United States as providing acceptable information and if so, what qualities are required for a lab outside of the US to be recognized (e.g., WHO or national reference center) by the Agency?

Lines 412 -415: *"We recommend that multiple clinical isolates be examined by phenotypic assays with the investigational drug and clinical isolates representative of the breath of diverse mutations and combinations know (if known) to confer reduced susceptibility."*

We suggest the Agency clarify "multiple clinical isolates" by providing a range for the number of isolates to be tested.

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IV. Proposal for Monitoring Resistance Development:

Lines 421-425: *"Given the importance of drug resistance in treatment decisions and the need to disseminate to health care providers information about an antiviral drug's resistance profile, it is strongly recommended that comprehensive resistance testing be undertaken in all phases of drug development."*

We recommend adding the phrase "consistent with the way the drug will be used" to the end of the sentence above so that it would read: "...testing be undertaken in all phases of drug development **consistent with the way the drug will be used."**

Lines 451-452: *"Time points that samples for viral loads, genotypic and phenotypic assays, and other resistance analyses will be collected (i.e., baseline, week 24, week 48, discontinuations)."*

The most important time point to be tested is following virologic failure. We suggest the information in the parentheses be revised as follows: (i.e., baseline, week 24, week 48, **following regimen failure or** discontinuation)

Lines 463-467: *"We suggest that genotypic and phenotypic analyses of baseline and post-treatment isolates be completed in a timely manner to characterize the resistance profile of the investigational drug and its cross-resistance potential with other antiviral drugs. Sponsors are strongly encouraged to collect (at a minimum) phenotype and genotype data for baseline isolates from all patients and endpoint isolates from all virologic failures and discontinuations (not suppressed).*

In this section is the Agency suggesting the need to **test** baseline and virologic failure or discontinuation samples from all patients? Samples should be collected and analyzed to the extent required to give an accurate and informative picture of the potential for resistance and cross resistance of the drug being evaluated in the circumstances of intended use.

VI. Summary

Lines 509-511: *"The preceding sections of this guidance include recommendations for how and when to perform nonclinical virology studies. Such information could potentially be included in drug labeling to facilitate appropriate prescribing of products and to maximize the chance for therapeutic success."*

For reasons mentioned earlier in this document we believe that the in vitro information included in product labels needs to include a caution as it is not always predictive of what will be seen in the clinic. There comes a point at which adding in vitro data to a label for a marketed product could be more confusing than helpful especially if it is not concordant with what has been seen in clinical studies with the antiretroviral combinations. We believe this section of the label should include a reference for physicians to refer to the clinical sections of the label.

Appendices

- We recommend the Agency include language suggesting that there is some degree of flexibility when it comes to completing the virus specific templates. The data provided in the templates must be consistent with the circumstances of the individual trials and the patient population

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studied (for example, it is unreasonable to request baseline HIV genotype and phenotype for patients who enrolled in a study with well controlled HIV and viral levels <1000 copies/mL).

- On the HCV template the term "HBV DNA" should be changed to "HCV RNA" everywhere it appears
- ***Lines 629, 637 and 645 (Mutation Count).*** The mutations the Agency is suggesting be counted focus on amino acid positions known already to be of key relevance to resistance, but the Agency does not specify precisely which substitutions should be counted [e.g., at protease position L90 the intent is presumably to capture the resistance-associated substitution L90M, but, since this is not specified, one might include a non-significant (natural) polymorphism such as L90F that happens to be present at this position in the isolate but which is not known to be associated with drug resistance]. Since the intent of this section is apparently to focus on the quantification of mutations associated with resistance, a lack of specificity around the identity of substitutions to be included could lead to misleading conclusions. Therefore, we recommend that either all changes at every amino acid position are counted, or that the Agency defines exactly which changes should be counted at the positions in the selected 'resistance mutation' positions, for example consistent with the current version of the IAS guidelines.

In conclusion, we appreciate the opportunity to comment on this guidance document. We have found this draft guidance very helpful in outlining the Agency's expectations with regard to the scope and timing of testing that should be done during the development program for an antiviral product. We believe the changes Roche is recommending in this set of comments will further enhance the clarity and value of the guidance document. Finally, while this guidance is particularly useful for products with well established targets, we trust that the Agency will be flexible in its application of these standards/principles to compounds which are developed for novel/emerging targets.

Should you have any questions regarding these comments please don't hesitate to contact the undersigned by phone at 973-562-3676 or fax 973-562-3700.

Respectfully Submitted,

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Enclosure (1)

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